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## REPORT

## New findings in Alzheimer's research

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Alzheimer's disease isn't afforded the luxury of time. Four million Americans are affected today, and those figures expected to double by 2030. Scientists are pressing for an accelerated pace in research to unravel this disease. Presently, there is no cure. But in laboratories around the world, scientists have been feverishly trying to fit together a puzzle to explain how Alzheimer's is caused, who's susceptible and how to diagnose, treat or prevent it altogether.

by Angela Pirisi

So far, what we know today is that Alzheimer's disease is characterized by plaques, fibrous tangles and nerve cell death, and these changes in the brain give way to neuronal degeneration and cognitive impairment. For decades now, scientists have theorized that the abnormal build-up of amyloid plaque in the brain forms the basis of the damage caused by Alzheimer's. In a normal, healthy brain, amyloid is produced, broken down and its debris is then cleared away to prevent it from piling up between brain cells. In the case of a brain under siege by Alzheimer's disease, the amyloid accumulates and hardens into insoluble plaques that, researchers suspect, are neurotoxic and may take their toll on mental functioning by upsetting nerve cell function, producing inflammation and killing nearby cells.



## Towards prevention

Drug experimentation with a view to treatment and prevention has been looking at anti-inflammatories (i.e. ibuprofen), statin cholesterol-lowering drugs, estrogen, acetylcholine (cholinesterase inhibitors) and nerve growth factor, as well as antioxidants (i.e. vitamin E). Ibuprofen and other anti-inflammatories, showed UCLA researchers, could help control both the inflammatory response to plaques as well as the number of plaques, and delay the onset of Alzheimer's by about a decade.(1) That might help prevent about 75% of cases, suggest the authors, based on the calculation that it takes plaques about 20 years to develop to the point where they impair memory and cognition, and the risk of Alzheimer's doubles every five years after age 65. To further explore the possibilities of anti-inflammatory drugs, the National Institute on Aging (NIA) launched a new clinical trial at the end of January 2001, called the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), to test naproxen and celecoxib (Celebrex) with regards to Alzheimer's prevention. As for estrogen, despite conflicting evidence to date, a 16-year study of 472 women—part of the Baltimore Longitudinal Study on Aging (BLSA)—showed that a history of estrogen replacement therapy (ERT) in women after menopause cut the risk of developing Alzheimer's disease in half.(2)



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Meanwhile, in the new US guidelines for Alzheimer's disease, recently released at the American Academy of Neurology annual meeting in Philadelphia (May 2001), vitamin E was said to "delay the time to clinical worsening," while cholinesterase inhibitors could "improve symptoms in mild-to-moderate Alzheimer's" patients.(3) It's been noted that people with Alzheimer's disease have lower brain levels of acetylcholine, a neurochemical that's involved in learning and memory functions.(4) Cholinesterase inhibitors work by blocking the enzyme (cholinesterase) that breaks down acetylcholine. Scientists are also studying the potential behind molecules called nerve growth factors to slow or prevent neurodegeneration, which may hopefully also offer a method of regenerating injured neurons.

#### Animal studies

Some of the latest big news in Alzheimer's research comes from the Massachusetts General Hospital, where investigators have found a way to destroy existing plaque deposits in the brain.(5) Using a transgenic mouse model (bred to develop Alzheimer's plaques), researchers were able to show the effectiveness of injecting anti-plaque antibodies into diseased brain tissue to dissolve beta-amyloid plaques. The scientists found that they could make 70% of pre-existing plaques disappear in just three days. This is the first time that anyone has been able to clear Alzheimer's plaques.

The study involved anaesthetizing transgenic mice and performing a craniotomy (drilling tiny holes into the skulls) to allow a passage for the injection of the antibodies into brain tissue. The researchers then injected three fluorescent tracers

to stain the plaques and the antibodies, as well as to provide a road map with local landmarks to help relocate the marked plaques. They relocated 80% of the initial plaques in control animals but only saw 30% of the plaques in the treated animals.

The study's findings are significant because they established two very important proof-of-principles. First off, they show for the first time that it is indeed possible to remove Alzheimer's plaques. The implications, if born out by future studies, could be that Alzheimer's progression is stoppable. The second important finding is that plaques can be reversed by the external application of antibodies rather than by mustering up the immune system army of T cells and B cells, as done with vaccination.

Stephen Snyder, Ph.D., Program Director, Etiology of Alzheimer's Disease, at the National Institute on Aging (NIA), which helped to fund the study, suggests that the findings don't have any immediate application, in that the research couldn't be replicated in human subjects—for ethical reasons. However, he says, "Future studies in diagnosis, treatment and prevention will point back to this paper as having given some direction for advances yet to come in those respective areas. This was a first step in literally showing that the antibody approach is an efficacious one." And even though the physical approach to delivery may not be relevant for treating Alzheimer's, Snyder adds, "An idea worth pursuing from these studies is that passive immunotherapy might effectively eliminate plaque from brain, and thereby limit any toxic effects on neurons stemming from the presence of the peptide." The key would be getting good penetration of the antibodies across the blood-brain barrier into the brain, which other studies have suggested to be possible.

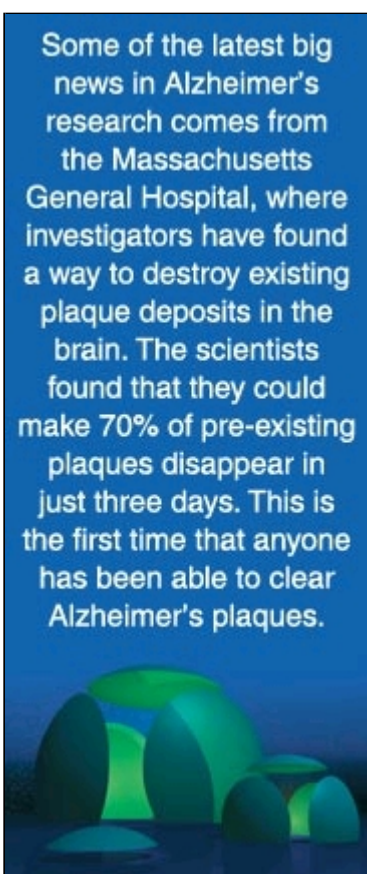
Another noteworthy point was that microglia, which are essentially macrophage-type cells found in the central nervous system, surrounded the remaining, uncleared plaques, suggesting that the antibodies had called the immune system to action, or that the antibodies' actions are perhaps mediated by the microglia. Activated microglia have long been suspected of having some kind of role to play in the initial stages of neurodegeneration in Alzheimer's. In this case, however, and as more recent studies show, microglia agents may help to control the plaques' build-up. As Snyder explains it, "It would appear that the old double-edged sword is at play here too— microglia may release factors that do harm and do good. It has long been appreciated that microglia can be found in the vicinity of diffuse and neuritic plaques, but it isn't really known what the actual role is of the microglia in the AD brain." Interestingly, researchers at the University of California, San Francisco (UCSF) recently reported findings that suggest activated microglia are not responsible for causing inflammation and spurring on disease progression as previously thought.(6) They found that a molecule called TGF- $\beta$ 1 (transforming growth factor beta1), which regulates the brain's responses to injury and inflammation, incites microglial cells to action to clear away amyloid deposits.

### Seeing plaques

The Massachusetts study also constitutes the first time that plaques have been observed in a living animal, thanks to the novel imaging technology used for conducting this research called the multi-photon microscope. These scientists had originally set out to develop novel imaging techniques that might help facilitate the possibility of early diagnosis in Alzheimer's.

Right now, there is no single proven laboratory diagnostic test for Alzheimer's disease. While Alzheimer's can be diagnosed with about 90% accuracy through physical and neuropsychological testing, combined with brain imaging, only an autopsy of the brain currently gives a 100% accurate diagnosis of the disease and a clear picture of its ravages. Conventional imaging techniques, such as a CT (computerized tomography) scan or MRI (magnetic resonance imaging) are currently used to try to nail down a diagnosis of Alzheimer's and to rule out other potential causes of dementia. Plaques, however, are too tiny to be seen with these typical imaging and scanning methods. But by using a multi-photon microscope, the investigative team was able to view the plaques in a living animal. Apparently, the multi-photon microscope can image more deeply and precisely inside tissue than conventional microscopes, because it focuses an intense beam of near infrared light on fluorescent marked tissue.

This study follows quickly on the heels of earlier research, which had shown that plaque formation could be prevented with a vaccine that charged up the immune system to keep the amyloid deposits at bay. Those scientists demonstrated that, by repeatedly administering an amyloid vaccine, it was possible to generate an immune response—the mice developed antibodies against the protein—to almost eliminate amyloid plaque formation in the test animals.(7) Preliminary safety testing in humans and the initial results of a phase I clinical trial of the vaccine showed that it's well tolerated in humans. Later, another set of scientists at Harvard Medical School(8) similarly proved the efficacy of an Alzheimer's vaccine to stave off plaque formation. They found that they could use another approach for administering the same amyloid protein vaccine nasally.



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## Amyloid—cause or effect?

The next question following quickly in the tracks of such discoveries is whether getting rid of the plaques would also result in regaining some cognitive and memory functions and perhaps preventing further loss of one's mental faculties. There are those who believe that plaques are the physical aftermath of Alzheimer's that mark its destructive path, and that removing them may be like picking a scab off a wound without getting rid of the infection below. Others are convinced that the plaques literally lay down the foundation for Alzheimer's disease to start up, in which case reversing them may be like removing bullets from a gun.

There is a great deal of research based on the latter speculation, which suggests that halting plaque formation and/or getting rid of existing plaques would aptly prevent or treat Alzheimer's. A number of studies have given hope by suggesting that this is the case, as Canadian researchers at the University of Toronto's Centre for Research in Neurodegenerative Diseases confirmed recently with their research, which involved testing cognitive ability in mice after administering an amyloid beta (Abeta) vaccine. Their results showed that dissolving about 50% of existing amyloid plaques does help to improve memory function, thereby lending support to findings by Schenk et al.(9) The authors write that, "Evidence that Abeta immunization also reduces cognitive dysfunction in murine models of Alzheimer's disease would support the hypothesis that abnormal Abeta processing is essential to the pathogenesis of Alzheimer's disease, and would encourage the development of other strategies directed at the 'amyloid cascade'." Moreover, the reduction in cognitive dysfunction was observed with removing just 50% of the plaques.

Similarly, findings by researchers at the University of South Florida showed that vaccination with Abeta protected transgenic mice from the learning and age-related memory deficits that normally occur in this mouse model for Alzheimer's disease.(10) Compared to untreated transgenic mice (controls), the inoculated mice showed better cognitive performance in a series of maze tests, and performed equally well as non-transgenic (non-Alzheimer's) mice.

## The research

Whether plaque prevention or removal yields any mental benefits is only part of the question being explored today. Some researchers are still stuck on answering what is the definitive cause of Alzheimer's disease. Since the 1980s, when it was discovered that tangles were made up of a protein called tau, and that plaques contained beta-amyloid, scientists have endlessly debated whether it's tau or beta-amyloid (also referred to as BAP) that's responsible for bringing on Alzheimer's. Explains Snyder, "One camp promotes the Abeta peptide and the processing of the amyloid precursor protein as the key player in the development and progression of AD, while the other has its sights set on the tau protein, its biochemistry and tau neuronal cell biology related to tau. The NIA has always supported and continues to support fundamental research in both of these areas. The recent (1998) discovery of the tauopathies, a class of neurodegenerative and dementia diseases caused by mutations in the tau protein, has fueled the debate still more."

## Finding more clues

The questions may be complex, but researchers have been making remarkable headway in piecing together this insidious disease and devising ways to combat it. In fact, while Alzheimer's research embarked on a humble journey two decades ago, the discoveries have come fast and furious since then. Dedicated scientists are learning increasingly more about the underpinnings of this disease by the day.

As far as determining risk factors, lots has been done in terms of weighing out the role of genetics. So far, scientists have identified several Alzheimer-associated genes, including amyloid precursor protein (APP), apolipoprotein E (apoE), presenilin 1 (PS-1) and presenilin 2 (PS-2). The latest findings with regards to APOE-4 (a mutated form of apolipoprotein E gene closely tied to Alzheimer's) are from a UCLA study, which showed that those carrying the Alzheimer's gene APOE-4 (ApolipoproteinE-4) had significantly lower function in specific areas of the brain located above and behind the temples, amounting to a 5% decline in brain functions at a two-year follow-up.

In support of the BAP argument, researchers at Rockefeller University recently attempted to settle the controversy surrounding how much plaque build-up correlates with dementia and whether Abeta changes precede or follow changes in tau. They managed to show that amyloid beta-peptide Abeta-containing plaques were elevated in cases of early dementia and strongly related to cognitive decline too.(11) In fact, state the authors, in the frontal cortex, Abeta was elevated even prior to the occurrence of significant tau pathology. They conclude by saying that Abeta plays an important role “in mediating initial pathogenic events in AD dementia and suggest that treatment strategies targeting the formation, accumulation or cytotoxic effects of Abeta should be pursued.”

Amyloid plaque is just one focal point in Alzheimer’s research, however, as scientists also consider the importance of many other factors that may be involved in the development or progression of the disease, such as the tau protein and neurofibrillary tangles in the brain. Also being weighed are genetics, hormones, inflammation and oxidative stress. Each new discovery, no matter how seemingly small in the context of ultimately finding a cure, furnishes scientists with a better picture of how the disease develops while aiding them in defining genetic and biologic changes that underlie AD, identifying high-risk individuals, finding possible drug targets, and homing in on what characterizes normal aging patterns in the brain and age-related cognitive decline. At the very least, the new research by Bacskai et al. gives hope to proponents of the amyloid theory that they are on the right track. The greater hope is that reducing plaque formation and/or reversing plaque deposits will one day help to design therapies aimed at preventing or delaying the symptoms of Alzheimer’s. Next, the researchers at Massachusetts General Hospital would like to establish the level and quality of brain function in areas that have been cleared of plaques, in hopes of understanding how to improve brain function.



With regards to drug targets, many researchers are focusing on developing therapeutic approaches that inhibit certain key proteases within cells, beta- and gamma-secretase, which are believed to be pivotal in the formation of beta-amyloid. Last year, at the Society for Neuroscience’s annual meeting in New Orleans, scientists from Johns Hopkins University reported findings that showed beta-secretase to be responsible for forming the molecules that make up plaque within the brain’s nerve cells. Using knockout mice missing genes for beta-secretase, these investigators demonstrated that nerve cells lacking the enzyme did not form the plaque protein (beta amyloid).

Meanwhile, researchers at the University of Toronto reported last year on finding a protein, which may serve as a potentially new drug target. They showed that a protein molecule named nicastrin seems to play a key role in regulating how APP becomes fragmented and leads to the deposition of plaques. Earlier work by the same scientists had uncovered presenilin-1 and presenilin-2, implicating the proteins in causing two of the most insidious forms of Alzheimer’s.

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